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Effectiveness and safety of IFN-free DAA HCV therapy in HIV/HCV co-infected persons: Results from a pan-European study

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Abstract

Objectives: To investigate the effectiveness, safety and reasons for premature discontinuation of direct-acting antivirals (DAAs) in a diverse population of HIV/HCV co-infected individuals in Europe.

Methods: All HIV/HCV co-infected individuals in the EuroSIDA study that started interferon (IFN) free DAA treatment between 1/6/2014 and 1/3/2018 with ≥12 weeks of follow-up after treatment stop were included in this analysis. Sustained virological response (SVR) was defined as a negative HCV-RNA result ≥12 weeks after stopping treatment (SVR12). Logistic regression was used to explore factors associated with SVR12.

Results: 1042 individuals started IFN-free DAA treatment after 1/6/2014 and were included, 862 (82.2%) had a known response to treatment, 789 (91.5%, 95% CI 89.7-93.4) of which achieved SVR12. There were no differences in SVR12 across regions of Europe (p=0.84). After adjustment, the odds of achieving SVR12 was lower in individuals that received sofosbuvir/simeprevir +/- RBV (aOR 0.21 (95% CI 0.08-0.53) or ombitasvir/paritaprevir/dasabuvir +/- RBV (aOR 0.46 (95% CI 0.22–1.00) compared to sofosbuvir/ledipasvir +/- RBV. 43 (4.6%) individuals had one or more components of their HCV regimen stopped early, most commonly due to toxicity (n=14); of these 14, 11 were treated with ribavirin. Increased bilirubin was the most common grade 3 or 4 laboratory adverse event (n=15.3%) and was related to treatment with atazanavir and ribavirin.

Conclusions: Our findings from real-world data on HIV/HCV co-infected individuals across Europe show DAA treatment is well tolerated, and that high rates of SVR12 can be achieved in all regions of Europe.

Keywords: HIV/HCV co-infection, DAA treatment, DAA safety, SVR, Europe

Introduction

Globally, 38 million people were estimated to have human immunodeficiency virus (HIV) by the end of 2019 [1]. Among these, 2.3 million individuals were also co-infected with hepatitis C virus (HCV) [2] including more than 700.000 individuals in the World Health Organisation (WHO) European Region [2]. In the absence of antiretroviral therapy, HIV co-infection accelerates fibrosis progression particularly in those with low CD4 cell counts [3, 4]. HIV treatment guidelines now recommend starting antiretroviral therapy (ART) at HIV diagnosis for all patients, but it is also important to identify and treat HCV early to prevent the progression to liver disease and onward transmission to others [5, 6].

With the advent of direct-acting antiviral (DAA) therapy against HCV, more than 95% of those included in phase 3 clinical trials achieve a sustained virological response (SVR) with similar high SVR rates reported in both HCV mono-infected [7-9] and HIV/HCV co-infected individuals [10-13]. An SVR is associated with a significant improvement in liver-related and all-cause mortality [14-16]. This revolution in HCV treatment prompted the WHO to adopt a list of targets to eliminate viral hepatitis as a public health threat by 2030. These targets include providing HCV treatment to 80% of eligible patients which will lead to cure in more than 90% of patients, and have a major impact on HCV-related mortality [17].

Randomised controlled trials remain the gold standard for drug approval, however, participants are generally highly selected and differ from the general population that will be receiving the treatment post licencing. So far, real-world data from national or local HIV/HCV cohorts from Western Europe and the US have shown SVR rates only slightly lower than reported in clinical trials [18-22], but data from demographically diverse populations in Europe, in particular Central and Eastern Europe are still

missing. Our study aimed to investigate the effectiveness and safety of DAAs in HIV/HCV co-infected individuals from the large pan-European EuroSIDA cohort study.

Methods

EuroSIDA study participants

EuroSIDA (http://www.chip.dk/Ongoing-Studies/EuroSIDA/About) is a large ongoing prospective observational cohort study that began enrolling HIV-1 positive patients in 1994. There are currently data on over 22000 HIV-positive individuals aged 16 or older from 100 centres in 35 European countries, Israel and Argentina. Since 1994, ten patient cohorts have been recruited through enrolment waves at regular intervals. While individuals in cohort one to nine were enrolled irrespective of HCV status, HIV positive individuals in cohort ten were also required to be anti-HCV positive (regardless of HCV-RNA status). At recruitment, demographic and clinical data is collected as well as complete ART history, CD4 count, HIV-RNA, anti-HCV, HCV-RNA, HCV genotype and hepatitis B surface antigen. Data are then collected prospectively at clinical sites and sent to the EuroSIDA coordinating centre at 12-monthly intervals (6 monthly until 2015). Where possible, participants continue to be followed if they transfer to another EuroSIDA clinic. Further details on the EuroSIDA cohort have been reported elsewhere [23], and can be found on the EuroSIDA website (https://www.chip.dk/Studies/EuroSIDA).

This analysis included all individuals under follow-up in EuroSIDA that received interferon-free DAA therapy after 1 June 2014, as this is when EuroSIDA began collecting detailed information about HCV treatment including data on reasons for early discontinuation and treatment-limiting toxicities of HCV therapy. All reported HCV treatment toxicities were reviewed by a clinician. Baseline was defined as the start date of DAA treatment. Individuals that did not have at least 12 weeks of follow-up after

completing DAA treatment were not included in this analysis (unless they died within 12 weeks of stopping treatment). Baseline characteristics were defined based on the most recent measurement prior to baseline. Fibrosis stage was defined using a consensus definition [24], and was based on the most recent fibrosis marker measured prior to the baseline. When more than one fibrosis marker was measured on the same day, then priority was given to a biopsy result, followed by transient elastography, AST to Platelet Ratio Index (APRI) score then finally a plasma hyaluronic acid result. Information on how fibrosis data is collected and defined in EuroSIDA has been specified elsewhere [25]. SVR12 was defined as undetectable HCV-RNA 12 weeks or later after stopping DAA treatment. Treatment failure was defined as detectable HCV-RNA at the first measurement at the end of treatment or later, or individuals that died before SVR could be determined. Analysis of laboratory adverse events (AEs) was carried out on individuals that started treatment between 1 June 2014 and 1 October 2016, as this is when data on laboratory values during therapy were systematically collected.

Statistical analysis

Baseline characteristics of individuals with a known treatment outcome were compared between those with and without SVR12, using the chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables. Reasons for stopping treatment early and AE were also described. Logistic regression was used to calculate the odds of having a known response to DAAs, and factors associated with achieving SVR12. Factors adjusted for were age, gender, region of Europe (South/Argentina, Central West, North, Central East, East; regions are defined in [23]), ethnicity, HIV risk group (MSM, IDU, other), CD4 nadir and baseline CD4 cell count (both as continuous variable (per 100/mm^3) and categorised as ≤500 , >500 (cells/mm^3), and unknown), baseline HIV-RNA (≤500 , >500 copies per mL, unknown), HCV treatment regimen, stage of liver fibrosis, HCV genotype, HCV-RNA (positive and unquantified, <500,000, ≥500,000 IU/mL) ever received cART (defined as at least three antiretroviral drugs from at least two drug classes) at baseline, prior HCV treatment, baseline date

(continuous (per 6 months later) and categorised as <2016 and ≥2016), treatment duration (continuous (per 1 week later) and categorised as ≤12 and >12 weeks), HBsAg, prior AIDS, prior non-AIDS defining event (malignancy, cardiovascular disease , end-stage liver disease, end-stage renal disease, and pancreatitis). Variables found to be associated with the outcome in univariable analyses ($p<0.1$) were included in multivariable models. The Division of AIDS (DAIDS) grading table was used to determine the severity of AEs for different biomarkers (haemoglobin, leukocytes, neutrophils, platelet count, s-creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin), where grade 1 indicates a mild event, grade 2 indicates a moderate event, grade 3 indicates a severe event, and grade 4 indicates a potentially life-threatening event [26]. SAS 9.4 was used for all analysis (version 9.4; SAS Institute, Cary, North Carolina, USA).

Results

Study population and treatment regimens

Among the 1234 individuals that started interferon-free DAA treatment between 1/6/2014 and 1/3/2018, 1033 individuals had at least 12 weeks of FU after ending treatment, and 9 individuals died within 12 weeks of stopping treatment, therefore 1042 individuals were included in this analysis (figure 1). Of the 1042 individuals, most received a DAA regimen consisting of sofosbuvir/ledipasvir +/- ribavirin (RBV) (n=501, 48.1%), 17.6% (n=183) received sofosbuvir/daclatasvir +/- RBV, 12.8% (n=133) received ombitasvir/paritaprevir/dasabuvir +/- RBV, 5.0% (n=52) received ombitasvir/paritaprevir +/- RBV, 4.7% (n=49) received sofosbuvir + RBV, and the remaining 11.9% (n=124) received other combinations of DAAs +/- RBV. Of the 1042 individuals included in this analysis, 379 (36.4%) had RBV included in their DAA regimen.

Virological response to treatment

Among the 1042 individuals included in this analysis, 789 (75.7%) individuals achieved SVR12; 73 (7.0%) were treatment failures (this included 9 deaths within 12 weeks of stopping treatment); 89 (8.5%) had a negative HCV-RNA result after stopping treatment but had no follow-up HCV-RNA result 12 weeks after stopping treatment; and 91 (8.9%) had an unknown treatment response. Therefore, 862/1042 (82.7%) individuals had a known response to their HCV treatment while 180/1042 (17.3%) had an unknown response. In multivariable analysis we found that individuals with an unknown treatment outcome were similar to those with a known treatment outcome, however the odds of having a known response to treatment was lower among individuals that started treatment in 2016 or later [adjusted odds ratio (aOR)=0.62, 95% confidence interval (CI) 0.43-0.88], and among those who had 'other' treatment regimens, and higher among individuals that received ombitasvir/paritaprevir/dasabuvir +/- RBV (compared to sofosbuvir/ledipasvir +/- RBV) [aOR=0.41, 95% CI=0.26-0.65 and aOR=2.05, 95% CI=1.06-3.98], respectively. In the univariable analysis, individuals from East/Central Eastern Europe (compared to Southern Europe) had a lower odds of having a known response to treatment (OR=0.5, 95% CI=0.31-0.79), however after adjusting for other variables the association was not as strong (aOR=0.63, 95% CI=0.38-1.04). Among the 862 individuals with a known response to treatment, 789 (91.5%, 95% CI 89.7-93.4) achieved SVR12 and 73 (8.5%) were treatment failures.

Baseline characteristics

Table 1 shows the baseline characteristics at time of starting HCV-treatment in the 862 individuals with a known SVR12 status. The majority were male (78.0%), of white ethnicity (89.3%), and had a median age of 51 years (interquartile range [IQR]: 45-55). The median CD4 count was 605 cells/mm^3 (IQR: 431-813), 94.9% of individuals had an HIV-RNA value ≤500 cp/ml and 96.9% had received cART. Of the 862 individuals with a known response, 772 (89.6%) had been genotyped. Genotype 1 was the most

common (64.2%), followed by genotype 4 (17.5%), genotype 3 (16.5%), and genotype 2 (1.8%). 817 (94.8%) individuals had at least one liver fibrosis marker recorded one year prior to their treatment start, 23.1% of which had cirrhosis (METAVIR stage F4). The proportion of individuals that achieved SVR12 was significantly lower in individuals with cirrhosis (p=0.012), with a SVR12 rate of 93.2% in those with METAVIR F0-F3, and 86.4% in those with cirrhosis. For the five most commonly used DAA regimens, the SVR12 rate was >90% in all except sofosbuvir/simeprevir +/- RBV where only 29/39 (74.4%) achieved SVR12. A total of 163 (18.9%) individuals had a previous non-AIDS defining illness (non-ADI). The most common non-ADI was end-stage liver disease (excluding hepatocellular carcinoma (HCC)) (n=58; of whom 32 [55.2%] also had cirrhosis), followed by cardiovascular disease (n=55), non-AIDS defining malignancy (excluding HCC) (n=46), pancreatitis (n=21), HCC (n=17), and end-stage renal disease (n=9). The proportion of individuals that achieved SVR12 was significantly lower among individuals that had a non-ADI compared to those that did not (86.5% vs 92.7%; p=0.0105). However, when ESLD was excluded from non-ADI, the difference was no longer significant (91.8% vs 90.0%, p=0.4962). The SVR rate in individuals with ESLD was 77.6%, compared to 92.5% in individuals without ESLD (p<0.0001).

Predictors of treatment response

The odds of achieving SVR12 was assessed in individuals with a known response to HCV-RNA treatment (n=862). After adjustment, factors found to decrease the odds of achieving SVR12 were having a non-ADI [aOR=0.53, 95% CI 0.0.30–0.95] and receiving sofosbuvir/simeprevir +/- RBV [aOR=0.21, 95% CI 0.08–0.53] or ombitasvir/paritaprevir/dasabuvir +/- RBV [aOR=0.21, 95% CI=0.08-0.53] compared to sofosbuvir/ledipasvir +/- RBV (Figure 2). While persons HCV-RNA positive but unknown level of viremia had lower rates of SVR12 (aOR 0.50, 95% CI 0.25–0.99), there were no differences between those with HCV-RNA levels quantified above or below 500,000 copies/mL. After excluding individuals with ESLD, the association between non-ADI and SVR12 was

no longer significant aOR=0.77, 95% CI 0.40-1.49. In contrast, ESLD was associated with lower SVR12 in both univariable and multivariable analysis [OR=0.28, 95% CI 0.14-0.55 and aOR=0.34 95% CI 0.16-0.74, respectively. In univariate analysis, those with cirrhosis (compared to fibrosis ≤F3) had lower odds of achieving SVR [OR=0.47, 95% CI=0.28-0.71], but after adjustment, cirrhosis was no longer associated with SVR12 [aOR 0.61 (0.34-1.09)]. In post-hoc, analysis we explored a potential interaction between risk group and region, however this was not significant (p>0.1). Age group, sex, ethnicity, region of Europe, HIV risk group, CD4 count, CD4 nadir, HIV-RNA, AIDS event, treatment duration (≤12 weeks vs >12 weeks), HCV genotype, cART, prior HCV treatment, and HBV co-infection were not included in the model as they either had p>0.1 in the univariable analysis (there was no evidence of an association with SVR12), or there was insufficient data to explore the association.

Reasons for stopping treatment early

Of the 1042 individuals included in this analysis, 934 (89.6%) individuals had information on whether they stopped treatment earlier than scheduled. Of these, 43 (4.6%) individuals had one or more components of their HCV regimen stopped early. Not all individuals stopped their entire treatment regimen, as 14 individuals only stopped RBV early. Of the 43 individuals that stopped treatment early, 24 (55.8%) achieved SVR12, 11 (25.6%) were treatment failures (including 4 deaths within 12 weeks of stopping treatment), and 8 (18.6%) had an unknown treatment response. The most common reason for stopping treatment early was reported adverse events (AEs) (n=14, 12 of which were on RBV). Among the 14 who stopped treatment early due to AEs, 11 stopped only RBV and completed the remaining DAA treatment as planned. 9 of these 11 had known response to treatment, of whom 8 (88.8%) achieved SVR12. The most common AE was anaemia (n=8), followed by, rash (n=2), neuropathy (n=1), tiredness, dizziness, anorexia (n=1), intolerance, rash, fatigue, and abdominal pain (n=1), and nausea and vomiting (n=1). Other reasons for stopping treatment early were substance abuse

(n=4), physicians decision (n=4), patients decision (n=2), virological failure (n=2), drug interaction (n=2), drug out of stock (n=1), or lost to follow-up (n=1), with 13 individuals having other/unknown reasons for stopping early. Two individuals died during treatment with cause of death reported as hepatitis with cirrhosis and an unspecified malignancy which was not HCC. An additional two individuals died within 12 weeks of stopping treatment, one due to HCC and the other with unknown cause of death. The median treatment time for those that stopped treatment early was 8 weeks (IQR 4-12). Those who stopped treatment early due to AEs were treated for a median of 9 weeks (IQR 4-14), and those with non-AE reasons for stopping treatment early were treated for a median of 8 weeks (IQR 4-12). Individuals who did not have any reported treatment interruption were treated for a median of 12 weeks (IQR 12-15).

Laboratory adverse events

Table 2 shows the number of individuals with pre-treatment laboratory AEs and during HCV treatment AE (graded 1 to 4) for different biomarkers. 555 individuals were eligible for this analysis as they started HCV treatment between 1/6/2014 and 1/10/2016. Of those eligible, 511 (92.1%) had laboratory data available during their treatment regimen and were included in this analysis.

Of the 511 individuals included in this analysis, 363 (71.0%) had at least 1 AE, and overall 770 AEs were recorded among them. The majority of AEs during treatment were grade 1 or 2 (n=651, 84.5%). The highest proportion of AEs during treatment was for elevated alkaline phosphatase (54.6%), followed by bilirubin (43.7%), and platelet count (28.6%), with a small proportion of individuals with neutropenia (1.3%) and leukopenia (3.0%). The most common grade 3 or 4 AEs during treatment was raised bilirubin levels (15.3%), followed by reduced platelet count (5.1%) and haemoglobin (1.6%), and increased alanine aminotransferase (ALT) (1.4%). Among those with a grade 3 or 4 ALT elevation,

one individual was HBsAg positive and received lamivudine as the only HBV active treatment. We do not have information about the HBV-DNA levels during HCV treatment. Of the 119 grade 3 or 4 AEs that occurred during treatment, 57.1% occurred in individuals on RBV. Also, 56.7% of the 67 individuals with a grade 3 or 4 bilirubin AE were on atazanavir and 65.7% received ribavirin. Among the individuals with grade 3 or 4 AEs, only two stopped their HCV treatment earlier than scheduled due to toxicity and none of them died during treatment.

Discussion

Results from this analysis including a large heterogenous population of HIV/HCV co-infected individuals across Europe receiving interferon-free DAA therapy in a real-world setting confirm the high SVR rates reported from other cohorts in Western Europe and the US [18-22]. Among participants where SVR12 could be determined, 91.5% achieved SVR which is only slightly less than reported in clinical trials [10-13].

Almost 20% of the persons who started HCV treatment did not have data to ascertain whether they achieved SVR12, although a significant number of these have an end of treatment response. Possible reasons include that HCV RNA was measured and not reported to EuroSIDA, or that HCV RNA has not been measured locally. The former is less likely given the rigorous quality assurance in place and that missing data has been requested by the coordinating team. Individuals with cirrhosis were less likely to achieve SVR12 in unadjusted analysis. After adjusting for confounders, we still saw a trend towards lower odds of SVR12 in those with cirrhosis, but the association was no longer statistically significant. We adjusted for previous non-ADI as a composite variable, but in a post-hoc analysis, those individuals with ESLD had lower odds of SVR12, which further indicates that cirrhosis influences the treatment outcomes negatively. The composite variable non-ADI includes any non-ADI prior to baseline, and among the 58 individuals that had ESLD, 25 also had another non-ADI. These

individuals may have more progressed disease and therefore it is possible that the association between ESLD and SVR12 may be partly attributable to confounding by indication. Findings from other large real-life cohort studies including the German Hepatitis C Cohort [22], a cohort of US veterans [20], and a co-infection registry in Madrid, Spain [19] all showed lower SVR12 rates among people with cirrhosis, whereas a French cohort study that included fewer individuals with cirrhosis (n=162) found no impact of cirrhosis on SVR12 [21]. We did not find any association between other HIV related factors (including HIV-RNA, CD4 cell count, use of ART or prior AIDS) again in agreement with other cohort studies [20-22]. In contrast, data from the Spanish co-infection registry that included 2,369 patients, found higher odds of HCV treatment failure among those with a prior AIDS defining disease and those with a CD4 cell count less than 200 cells/mm^3 which indicates that a subgroup of co-infected individuals with advanced HIV disease may have sub-optimal HCV treatment outcomes, but further studies are warranted to confirm these findings [19].

Our study is one the first to present data on patients from Central-East and Eastern Europe. The SVR rates were above 90% in all regions and there was no evidence of regional differences in SVR.Data from Central-East and Eastern Europe are still limited, and further investigation is warranted.

Among the five most commonly used DAA regimens, only the combination of sofosbuvir and simeprevir showed SVR rates less than 90%. Compared with sofosbuvir/ledipasvir, participants on sofosbuvir/simeprevir and ombitasvir/paritaprevir/dasabuvir +/- RBV also had significantly lower odds of SVR after adjustment. Lower SVR rates for sofosbuvir/simeprevir are also in agreement with findings from the Madrid co-infection registry [19] whereas this and another large real-life study did not find lower SVR rates among those receiving ombitasvir/paritaprevir/dasabuvir [19, 20]. The combination of sofosbuvir and simeprevir is no longer recommended by European HCV treatment guidelines for HIV infected persons, whereas ombitasvir/paritaprevir/dasabuvir is considered an

alternative treatment option [27]. There were no differences in the odds of SVR12 comparing those with high or low HCV RNA levels (based on a cut-off of 500,000 copies/mL)

The majority of individuals completed their HCV treatment as scheduled, with only 4.1% known to have stopped one or more drugs of the treatment regimen early. A third of all premature treatment stops were due to toxicity and in most cases (11 out of 14) ribavirin was the only drug in the regimen that was stopped due to well-known RBV adverse effects. The majority went on to achieve SVR12 after stopping RBV. Depending on DAA regimen, RBV is often added if cirrhosis is present, in which case the individual may be more at risk of an adverse event [27].

Laboratory AEs were seen in 71% during treatment, with 15.5% of all AEs being grade 3 or 4 AE. None of the individuals with grade 3 or 4 AEs died during or shortly after treatment and only two of them stopped treatment early because of AEs. Most of the grade 3 or 4 AEs were caused by elevated bilirubin especially when DAAs were concomitantly used with RBV and/or HIV therapy that included the protease inhibitor atazanavir, both of which well-known risk factors for elevated bilirubin [28, 29]. The low rates of serious laboratory adverse events are in agreement with data from clinical trials [10, 13, 30] whereas other real-world studies have not reported these events systematically [19-22].

A major strength of this study is that it provides longitudinal clinical cohort data on a large number of individuals across different regions in Europe in a standardised way, which allows for comparisons between regions and examination of changes over time. In addition, all individual treatments and reasons for treatment discontinuation has been centrally reviewed. Our study is also one of the first to include data from East and Central East Europe. However, some of our findings should be interpreted with caution. Firstly, we were not able to determine SVR12 for 18% of individuals included in this

analysis as we did not have HCV-RNA follow-up data. A proportion of these were known to have end of treatment response and it is worth noting that these are real world data and not all individuals attend at set timepoints to assess SVR, nor do all clinics have resources to test. Not all individuals had data on whether they completed their treatment regimen, however we repeated the analyses among those with information on whether they completed treatment, and found the results to be consistent. Also, we may have underestimated the number of individuals who stopped due to toxicities, as some centres included physician's decision and patient's decision as reasons for stopping treatment early, which may have overlapped with toxicities. We only systematically collected lab data during treatment for individuals that started treatment between 1/6/2014 and 1/10/2016 which prevented us from evaluating AEs of more recently approved DAA drugs. Also, those with laboratory data and assessed for AEs were significantly different from those without lab data and excluded from this analysis. Finally, the EuroSIDA cohort may not be representative of HIV/HCV co-infected individuals in general as it mainly collects data from university clinics in large European cities.

In conclusion, our analysis of a large European longitudinal clinical cohort showed similar rates of SVR12 to results from other real-life cohorts and only slightly lower SVR12 rates than in clinical trials. This confirms the effectiveness and safety of DAA therapy in HIV/HCV co-infected individuals, and supports current treatment recommendations to treat all HCV infected individuals, regardless of co-infection with HIV.

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Figure 1. Flowchart for inclusion of individuals into analysis

Figure 2: Factors associated with achieving SVR

*Non-ADI: non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, HCC, end-stage renal disease, pancreatitis

†Either a biopsy (METAVIR stage F4), FibroScan (>12.5kPa), APRI (score >2), or hyaluronic acid (>250ng/mL) at baseline

Table 1: Baseline characteristics at time starting treatment in individuals with known SVR12 status

		Overall	SVR	Treatment failure	P-value
		n (%)			
Overall		**862 (100.0)**	**789 (91.5)**	**73 (8.5)**	
Sex	Male	672 (78.0)	612 (91.1)	60 (8.9)	0.361
	Female	190 (22.0)	177 (93.2)	13 (6.8)	
Ethnicity	White	770 (89.3)	715 (92.9)	55 (7.1)	0.0003
	Global majority	25 (2.9)	22 (88.0)	3 (12.0)	
	Unknown	67 (7.8)	52 (77.6)	15 (22.4)	
Region of Europe	South/Argentina	341 (39.6)	309 (90.6)	32 (9.4)	0.838
	Central - West	287 (33.3)	264 (92.0)	23 (8.0)	
	North	117 (13.6)	107 (91.5)	10 (8.5)	
	East/Central - East	117 (13.6)	109 (93.2)	8 (6.8)	
HIV risk group	MSM*	204 (23.7)	190 (93.1)	14 (6.9)	0.141
	IDU†	473 (54.9)	425 (89.9)	48 (10.1)	
	Other	185 (21.5)	174 (94.1)	11 (5.9)	
HIV-RNA (cp/ml)	≤500	818 (94.9)	747 (91.3)	71 (8.7)	0.423
	>500	10 (1.2)	9 (90.0)	1 (10.0)	
	Unknown	34 (3.9)	33 (97.1)	1 (2.9)	
Non-ADI†	No	699 (81.1)	648 (92.7)	51 (7.3)	0.010
	Yes	163 (18.9)	141 (86.5)	22 (13.5)	
DAA regimen	Sofosbuvir/ledipasvir +/- RBV	423 (49.1)	399 (94.3)	24 (5.7)	0.002
	Sofosbuvir/daclatasvir +/- RBV	155 (18.0)	140 (90.3)	15 (9.7)	
	Ombitasvir/paritaprevir/dasabuvir +/- RBV	121 (14.0)	109 (90.1)	12 (9.9)	
	Ombitasvir/paritaprevir +/- RBV	39 (4.5)	37 (94.9)	2 (5.1)	
	Sofosbuvir/simeprevir +/- RBV	39 (4.5)	29 (74.4)	10 (25.6)	
	Other	85 (9.9)	75 (88.2)	10 (11.8)	
Baseline date	<2016	477 (55.3)	430 (90.1)	47 (9.9)	0.104
	≥2016	385 (44.7)	359 (93.2)	26 (6.8)	
Fibrosis‡	F0-F3	618 (71.7)	576 (93.2)	42 (6.8)	0.012
	F4	199 (23.1)	172 (86.4)	27 (13.6)	
	Unknown	45 (5.2)	41 (91.1)	4 (8.9)	
HCV genotype	G1	496 (57.5)	459 (92.5)	37 (7.5)	0.564
	G2	14 (1.6)	13 (92.9)	1 (7.1)	
	G3	127 (14.7)	116 (91.3)	11 (8.7)	
	G4	135 (15.7)	122 (90.4)	13 (9.6)	
	Unknown	90 (10.4)	79 (87.8)	11 (12.2)	
Ever received cART	No	30 (3.5)	27 (90.0)	3 (10.0)	0.735
	Yes	832 (96.5)	762 (91.6)	70 (8.4)	
Prior HCV treatment	No	501 (58.1)	461 (92.0)	40 (8.0)	0.547
	Yes	361 (41.9)	328 (90.9)	33 (9.1)	
HCV-RNA (IU/ml)	<500000	195 (22.6)	179 (91.8)	16 (8.2)	0.017
	≥500000	462 (53.6)	432 (93.5)	30 (6.5)	
	Positive (unknown value)	205 (23.8)	178 (86.8)	27 (13.2)	
		Median (IQR)			
Age (years)		51 (45-55)	51 (45-55)	52 (46-54)	0.244
CD4 count (cells/mm^3)		605 (431-813)	612 (433-822)	580 (380-747)	0.092
CD4 nadir (cells/mm^3)		160 (72-265)	160 (70-265)	180 (77-264)	0.525

Table 2: Number of laboratory adverse events during treatment by grade

Biomarker	Baseline		During treatment								
			Individuals with data	AEs	Grade				Grade 3 or 4 AE		
	Individuals with data	AEs			1	2	3	4	Overall	On RBV	On ATZ*
Haemoglobin (g/dL)	385	4 (1.0)	451	43 (9.5)	26 (5.8)	10 (2.2)	6 (1.3)	1 (0.3)	7 (1.6)	4 (57.1)	1 (14.3)
Leukocytes (cells/mm^3)	334	4 (1.2)	365	11 (3.0)	8 (2.2)	1 (0.3)		2 (0.5)	2 (0.5)	1 (50.0)	
Neutrophils (cells/mm^3)	193	1 (0.5)	227	3 (1.3)	2 (0.9)			1 (0.4)	1 (0.4)	1 (100.0)	
Platelet count (cells/mm^3)	403	102 (25.3)	493	141 (28.6)	63 (12.8)	53 (10.8)	24 (4.9)	1 (0.2)	25 (5.1)	11 (44.0)	7 (28.0)
S-creatinine (mg/dL)	364	26 (7.1)	450	39 (8.7)	19 (4.2)	15 (3.3)	3 (0.7)	2 (0.4)	5 (1.1)	1 (20.0)	1 (20.0)
ALT† (IU/L)	399	234 (58.6)	488	95 (19.5)	70 (14.3)	18 (3.7)	5 (1.0)	2 (0.4)	7 (1.4)	4 (57.1)	3 (42.9)
AST‡ (IU/L)	392	189 (48.2)	463	74 (16.0)	62 (13.4)	10 (2.2)	(0.0)	2 (0.4)	2 (0.4)	1 (50.0)	
ALP§ (IU/L)	275	134 (48.7)	315	172 (54.6)	152 (48.3)	17 (5.4)	3 (1.0)		3 (1.0)	1 (33.3)	
Bilirubin (mg/dL)	367	91 (24.8)	439	192 (43.7)	71 (16.2)	54 (12.3)	50 (11.4)	17 (3.9)	67 (15.3)	44 (65.7)	38 (56.7)

Grades: 1 – mild, 2 – moderate, 3 – severe, 4 – potentially life-threatening

*ATZ: Atazanavir, †ALT: Alanine aminotransferase, ‡AST: Aspartate aminotransferase, §ALP: Alkaline phosphatase

When multiple measurements recorded during treatment, the lowest value was included for haemoglobin, leukocytes, neutrophils, platelet count, and highest value was included for s—creatinine, ALT, AST, ALP and bilirubin

Figure 1. Flowchart for inclusion of individuals into analysis

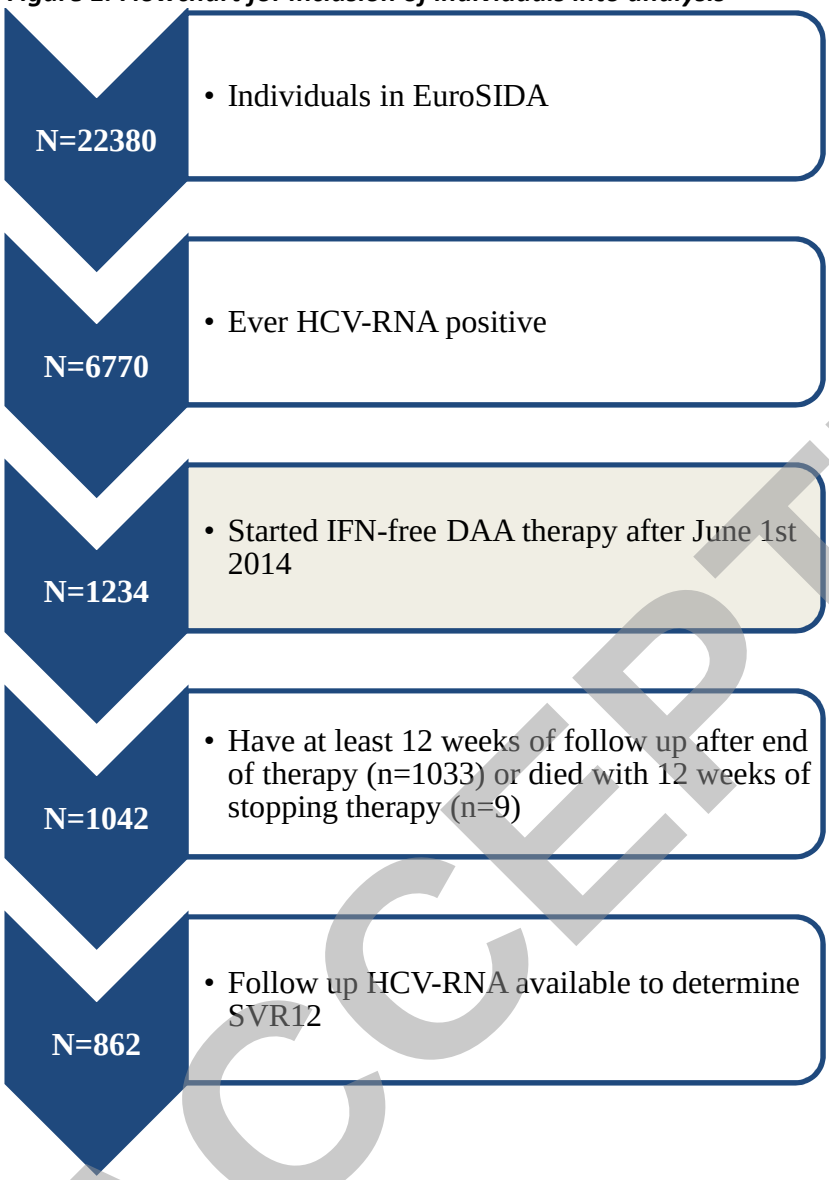
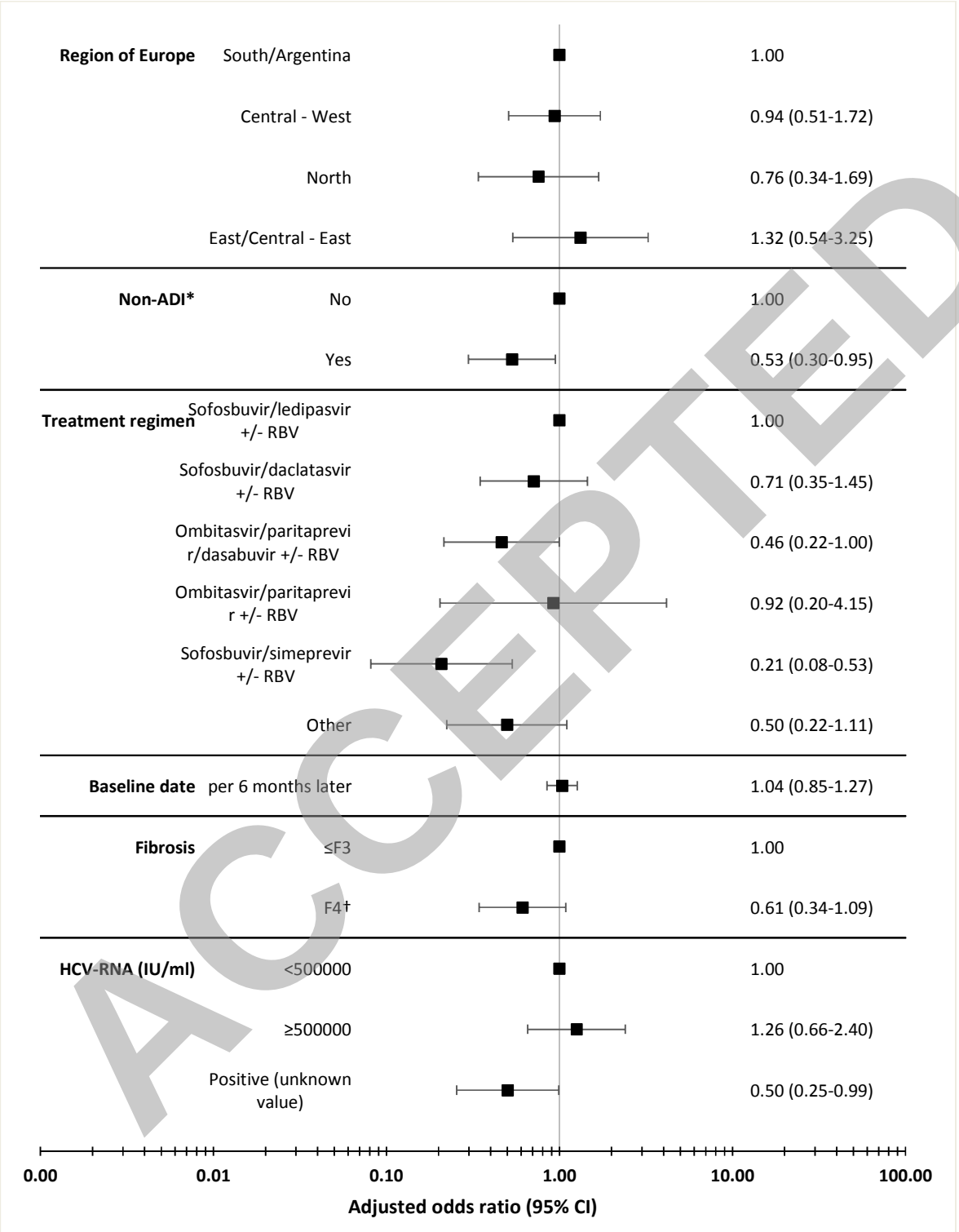


Figure 2: Factors associated with achieving SVR



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